REMARKS

Claims 1-29 were pending in the application. Claims 1-18 and 27-29 have been cancelled, claims 19 and 21-23 have been amended, and new claims 30-34 have been added. Accordingly, following entry of the amendments presented herein, claims 19-26 and 30-34 will be pending.

Claims 19, and 21-23, which originally depended on a non-elected claim (*i.e.*, claim 8), have been rewritten in independent form, *i.e.*, to specify that the polypeptide of the claimed method is a "SMRTe" polypeptide, *i.e.*, a SMRT-*extended* polypeptide, which, as defined in the specification, has the features previously recited in claim 8. In addition, newly added claims 30-34 further specify that the SMRTe polypeptides of the method are encoded by nucleic acids capable of hybridizing to a specific nucleic acid sequence recited in the claim under stringent conditions or have a specific percent amino acid identity with polypeptide sequences recited in the claims, as well as "gene transcription repressor activity" (*i.e.*, in claims 30-31). Support for the amendments and newly added claims can be found throughout the specification, and for example, at page 12, line 25, to page 13, line 14, at page 19, lines 20-23, and in Figures 1 and 5. Accordingly, no new matter has been added to the application by way of these amendments.

The foregoing claim amendments have been made solely for the purpose of expediting prosecution of the present application and should in no way be construed as an acquiescence to any of the Examiner's rejections in this or in any former Office Action issued in the present application. Applicants reserve the right to pursue the subject matter of the present claims prior to being amended herein in this application or in another related application.

In view of the foregoing claim amendments and the arguments set forth below, Applicants respectfully submit that the claims are now in condition for allowance.

Objections to the Specification

The specification is objected to because, according to the Examiner, "the title of the invention is not descriptive." The Examiner has requested a new title "that is clearly indicative of the invention to which the claims are directed."

Accordingly, Applicants have amended the title of the application to be clearly indicative of the claimed invention, thereby obviating the objection.

Objections to the Information Disclosure Statement

The Examiner has objected to the citation format of references A1 and A2 of the Information Disclosure Statement filed in connection with this case on February 27, 2003. Applicants submit herewith a replacement PTO Form SB/08, corresponding to the one filed, that

further lists a publication date and an author for the A1 and A2 references, as required by the Examiner.

Applicants respectfully request that the Examiner initial the replacement PTO Form SB/08 submitted herewith, and return a copy of the initialed form to the Applicants to signify that the aforementioned references have been considered and made of record.

Rejection of Claims 19-26 for Lack of Enablement Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 19-26 under 35 U.S.C. §112, first paragraph, as encompassing subject matter which is not described in the specification in such a way that one of ordinary skill in the art at the time of filing could have made or used the claimed invention without undue experimentation. Specifically, the Examiner is of the opinion that the specification, while being enabling for methods using a SMRTe polypeptide as provided in SEQ ID NO: 2, is not enabling for SMRTe polypeptide fragments thereof, SMRTe polypeptides that hybridize to a SMRTe cDNA, or SMRTe polypeptides having only 50% homology (para. 2, page 3).

Applicants respectfully disagree. The relevant inquiry with respect to enablement is whether the specification provides ample guidance to have enabled one of ordinary skill at the time of the invention to have made and used the presently claimed *method* without undue experimentation.

Methods for making polynucleotides encoding additional SMRTe polypeptides using, for example, genetic engineering, *e.g.*, restriction enzyme digestion and ligation, PCR, or chemical synthesis of polynucleotides using automated DNA synthesizers, are described in the specification (*e.g.*, at page 14, line 7, to page 26, line 1) and in the working examples (see, *e.g.*, Example 3, Fig.. 5).

The specification also provides more than ample guidance on how to make and use such SMRTe polypeptides, along with multiple working examples illustrating several different types of assay methods using additional SMRTe polypeptides, which would have enabled the skilled artisan at the time of the invention to have practiced the claimed invention without undue experimentation (see, *e.g.*, Examples 3 and 6).

Moreover, in the subsection entitled "Identification and Characterization of SMRTe cDNAs" (pages 79-82), Applicants describe in detail the structure and function of SMRTe polypeptides and in particular, the relevant SMRTe domains and the function of these domains. For example, the SMRTe polypeptides of the method are defined as comprising, *e.g.*, an N-terminal domain between amino acid residues 1 and 1111, or portions thereof, and in particular, a conserved domain between SMRTe and N-CoR termed the SMRTe and N-CoR conserved

(SNC) domain as well as having other functional domains such as, *e.g.*, several SANT domains. Importantly, the SMRTe polypeptides are described as having a common functional characteristic such as gene transcription repressor activity, *i.e.*, SMRTe activity, and this repressor activity has been demonstrated by Applicants, in living cells, for at least seven SMRTe polypeptides, or polypeptide fragments thereof (see, *e.g.*, Example 3 and Fig. 5). Moreover, this characteristic of SMRTe polypeptides is recited in the claims (*e.g.*, claim 24). In addition, newly added claims 30-34 specify that the SMRTe polypeptides of the claimed methods have sequence identity to SEQ ID NO: 2 (human SMRTe) (or fragments thereof), hybridize to a human SMRTe nucleic acid (*i.e.*, SEQ ID NO: 3) under high stringency conditions, or comprise actual portions of SEQ ID NO: 2, and these features are recited in the claims.

Armed with the above information, one of ordinary skill in the art at the time of the invention clearly could have prepared and used, without undue experimentation, the SMRTe molecules disclosed in the presently claimed methods.

For at least these reasons, Applicants respectfully request withdrawal of the rejection of claims 19-26 for lack of enablement under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 19-26 for Lack of Written Description Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 19-26 under 35 U.S.C. § 112, first paragraph, as encompassing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that Applicants, at the time the application was filed, were in possession of the claimed invention. Specifically, the Examiner asserts that the claims, which read on a method that uses SMRTe polypeptides does not "indicate what distinguishing attributes are shared by the members of the genus" or provide a "description of the conserved regions which are critical to the structure and function of the genus claimed".

Applicants respectfully disagree, and submit that the written description provided in Applicants' specification more than reasonably conveys to the skilled artisan that Applicants were in possession of the claimed invention, *i.e.*, a method of using SMRTe molecules for identifying modulators of SMRTe activity, at the time of filing.

The relevant inquiry for written description is whether the specification describes a sufficient number of representative polynucleotides encoding SMRTe polypeptides and/or a sufficient description of the correlation between the structure and function of the claimed class of SMRTe polypeptides, for use in the claimed methods to demonstrate to one of ordinary skill in the art that Applicants had *possession* of the claimed invention. Applicants believe the specification does provide the requisite written description.

As the Examiner is aware, in *The Regents of the University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), one of the issues addressed by the Court of Appeals for the Federal Circuit was the sufficiency of a disclosure in meeting the written description requirement of 35 U.S.C. §112, first paragraph, for claims to a genus of molecules, *i.e.*, cDNAs. The Court stated that:

> [a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.

Similarly, the Patent Office in its Guidelines[1] has determined that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics...*i.e.*, complete or partial structure, other physical and/or chemical properties, *functional characteristics* when *coupled with a* known or disclosed

[1] Guidelines for Examination of Patent Applications Under the 35 U.S.C. §112, ¶1, "Written Description" Requirement, 66 Fed. Reg. 1099 (January 5, 2001).

correlation between function and structure, or some combination of such characteristics" (emphasis added).

Applicants describe in their specification at least seven representative species of polynucleotides encoding SMRTe polypeptides that fall within the claimed methods using a class of SMRTe polypeptides. The specification defines a SMRTe polypeptide as structurally comprising, *e.g.*, an extended N-terminal region, of up to 1111 amino acids, and having several domains which can modulate gene expression in cells. As mentioned above, in Example 3, Applicants make seven (7) SMRTe polypeptide variants comprising this extended N-terminal region (or portions thereof) and demonstrate that these mutants modulate gene expression in living cells (see, *e.g.*, Example 3, Fig. 5).

In addition, the specification provides an extensive description of the structural features common to the SMRTe polypeptides. In particular, the common structures of the representative species of the genus of SMRTe polypeptides are shown, schematically, in Figs 2, 3, and 5. A description of the extended domain is provided in Figure 2 and described as a region of approximately 1,111 amino acids at the N-terminus (page 83, lines 9-27) of the polypeptide. The specification describes the modulatory activity, *e.g.*, transcriptional repression as provided by one or more portions of the N-terminal 1,111 amino acids of the SMRTe polypeptide (*Id.*). The specification also provides the polynucleotide sequence (SEQ ID NOS: 1, 3) and polypeptide sequence (SEQ ID NO: 2) of a human SMRTe molecule, the polynucleotide and polypeptide sequence of a murine SMRTe molecule (SEQ ID NOS: 4-6), as well as numerous portions of the N-terminal region of SMRTe molecules having SMRTe activity, *e.g.*, gene transcription repressor activity (see, *e.g.*, amino acid residues 1 to 165 of SEQ ID NO: 2, amino acid residues 165 to 305 of SEQ ID NO: 2, amino acid residues 165 to 665 of SEQ ID NO: 2, amino acid residues 435 to 936 of SEQ ID NO: 2, amino acid residues 725 to 906 of SEQ ID NO: 2, amino acid residues 889 to 973 of SEQ ID NO: 2, and amino acid residues 1 to 1111 of SEQ ID NO: 2; as described in Example 3, Fig. 5).

Moreover, in newly added claims 30-34, the SMRTe polypeptides of the claimed methods are encoded by a nucleic acid that hybridizes under stringent conditions to a SMRTe nucleic acid disclosed in the specification or as having high homology with SMRTe polypeptides disclosed in the working examples, and these features are expressly recited in the claims.

Importantly, Applicants clearly describe a number of SMRTe molecules by their structure and correlate such structure with function such as gene transcription repressor activity and this feature is recited in the claims (*i.e.*, claims 30-32). Accordingly, for carrying out the method of the invention, which is directed at identifying modulators of SMRTe polypeptides in cells, Applicants have met the written description requirement, both by describing a sufficient

representative number of SMRTe polypeptides and *by correlating common structural features of the polynucleotides with function.*

Thus, the exemplified polypeptides all fall within the claimed genus and serve as representative species that evidence possession of the genus of the claimed methods, as required under *Eli Lilly.*

For at least the foregoing reasons, Applicants respectfully request withdrawal of the rejection of claims 19-26 for lack of written description under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 19-26 for Indefiniteness Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejects claims 19-26 under 35 U.S.C. §112, second paragraph, as being indefinite because the claims recite the terms "stringent conditions" and "naturally occurring" without any further limitation, thereby rendering the claims unclear.

Applicants respectfully disagree. The term "naturally occurring" is art recognized and well defined in the specification as being, *e.g.*, a "nucleic acid molecule [that] encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2 [human SMRTe (extended], wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising SEQ ID NO: 1 or 3 under stringent conditions" (page 5, lines 23-26). The specification further specifies that "[f]unctional allelic variants [that] are naturally occurring amino acid sequence variants of the human SMRTe" and they functionally "maintain the ability to bind a SMRTe ligand, *e.g.*, a nuclear hormone receptor...[and]...contain only conservative substitution of one or more amino acids of SEQ ID NO: 2 or 5 or substitution, deletion, or insertion of non-critical residues in non-critical regions of the protein" (page 18, lines 1-7).

Similarly, the term stringent conditions, when referring to the hybridization of nucleic acids, is art recognized and further described in the specification as comprising conditions such that "sequences [of] at least about 60%, even more preferably at least about 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more [are] homologous to each other [and] typically remain hybridized to each other" (page 19, lines 14-17). In particular, the hybridization of nucleic acids is described in the specification as "hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2 X SSC, 0.1% SDS at 50°C, preferably at 55°C, more preferably at 60°C, and even more preferably at 65°C" (page 19, lines 20-23).

Without acquiescing to the Examiner's rejection, however, Applicants note that the claims, as now amended, no longer recite the term "naturally occurring" and where the claims do recite "stringent conditions", for example, in claim 30, the term has been fully defined within the

claim to further recite that the stringent conditions are carried out in "in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by at least one or more washes at 50°C to 65°C".

For at least these reasons, Applicants respectfully request withdrawal of the rejection of claims 19-26 under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 19-26 for Lack of Novelty Under 35 U.S.C. § 102(b)

The Examiner rejects claims 19-26 under 35 U.S.C. §102(b) as being anticipated by Evans *et al.* (WO 97/09418); hereafter "Evans"). The Examiner characterizes Evans as teaching the amino acid sequence of a SMRT polypeptide that is 57.5% identical to a polypeptide of the invention and methods of identifying compounds that bind to such polypeptides, thereby anticipating the claimed invention.

Applicants respectfully disagree. As amended, the present claims are drawn to methods that employ SMRTe polypeptides which, as defined in the specification, are distinct from SMRT polypeptides in that they, *inter alia*, comprise a large N-terminal extended region of structural and functional significance, or a portion thereof. The structure and function of this feature of the SMRTe polypeptides used in the methods of the invention, is clearly described in the specification, *e.g.*, in Examples 1 and 3.

By contrast, the SMRT polypeptide of Evans simply lacks the structural and functional features of the SMRTe polypeptides of the claimed invention. Moreover, claims 30-34 specify that the polypeptide of the claimed methods be at least 60% identical (or more) to the polypeptide sequence of human SMRTe (SEQ ID NO: 2) or be encoded by a nucleic acid which hybridizes to the nucleic acid encoding human SMRTe (SEQ ID NO: 3) under high stringency conditions which selects for a molecule having the structural and functional features of the SMRT-extended polypeptides used in the claimed methods.

Importantly, because the SMRT molecules of Evans are not the SMRTe, *i.e.*, SMRT-extended molecules disclosed in the instant application, any methods taught by Evans using only SMRT molecules simply can not teach each and every limitation of the claimed invention because the polypeptides used in the methods the Examiner is attempting to compare are structurally and functionally different.

Thus, because Evans fails to teach a method having the features of the claimed invention, Applicants respectfully request that the rejection under 35 U.S.C. §102(b), be withdrawn.

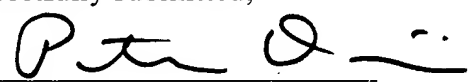
CONCLUSION

In view of the foregoing, entry of the amendments and remarks herein, reconsideration and withdrawal of all rejections, and allowance of the instant application with all pending claims are respectfully solicited. If a telephone conversation with Applicants' attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' attorney at (617) 227-7400.

An extension of time and appropriate fee is being filed herewith. If any additional fees are due, please charge our Deposit Account No. 12-0080, under Order No.UMY-030 from which the undersigned is authorized to draw.

Dated: August 4, 2004

Respectfully submitted,

By 

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